REMARKS

Claims 1-18, 27, and 28 are pending in the application. Claims 1, 2, 8, 10, 13-18, 27, and 28 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claim 12 has been canceled. Claims 3-7, 9, and 11 are currently being examined on the merits.

Claim 3 and Claim 9 have been amended to correct a typographical error that was introduced in the amendment dated 3/18/03. No new matter has been added by these amendments. The amended claims put the application in condition for allowance and/or remove issues for appeal; therefore, entry of these amendments is proper and is respectfully requested.

Withdrawal of previous rejections

Applicants would like to thank the Examiner for withdrawing previous rejections stated in the last Office Action. Applicants believe that with the amendments offered in this response and the remarks made herein, the remaining rejections should also be withdrawn.

Enablement rejections under 35 U.S.C. § 112, first paragraph:

Claims 3-7 and 9 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. This rejection of these claims is improper as the specification does adequately describe the invention so that it may be made and/or used by one of skill in the art.

The Examiner asserts that "the claims 3 and 9 were amended to recite that the biologically active fragment has 'serine hydratase' activity" and that "SEQ ID NO:1 is taught to have 'serine dehydratase' activity not 'serine hydratase' activity" (Final Office Action, p.3). Applicants submit that this was merely a typographical error contained in the amendment filed 3/18/03, an error that the present amendments correct. Claims 3 and 9, as amended herein, recite "a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine dehydratase activity." The response filed on 3/18/03 (pp. 6-7) further cites support in the specification for serine dehydratase activity *not* serine hydratase activity. This supports

Applicants' present assertion that the previous amendment filed 3/18/03 to claims 3 and 9 to recite "serine hydratase" activity was a typographical error.

With respect to the claimed variants, the Examiner asserts that "while one can screen for enzymatic activity the claims encompass variants that are 90% identical that do not function ... and as such one would not know how to use such polynucleotides" (Final Office Action, p. 3). Applicants respectfully reiterate that the claims are to polynucleotides, not the polypeptides that they encode, and therefore it is the use of the polynucleotides that is relevant. The specification recites many instances where a polynucleotide may be used, in which one of skill in the art would recognize that useful SDHH-encoding polynucleotides would encompass those encoding SDHH or its naturally-occurring variants, whether or not those encoded polypeptides had enzymatic activity.

For example, "the nucleotide sequences encoding SDHH may be useful in assays that detect the presence of associated disorders" (specification, p. 36, lines 18-19). The specification (p. 25, lines 16-18) discloses that "SDHH is expressed in tissues which are cancerous, proliferating, or involved in immune response. Therefore, SDHH appears to play a role in disorders of metabolism and cancer." Thus, these polynucleotide sequences may be utilized in assays to detect the presence of metabolism disorders or cancer. The specification further (p. 35, lines 9-11) discloses that "[t]he polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of SDHH may be correlated with disease." Indeed one of skill in the art would recognize that whether or not the polynucleotide encoded an SDHH protein having enzymatic activity, the use of the polynucleotide would be the same.

In another example, the polynucleotides are used as research tools. The specification (p. 35, lines 22-23) discloses that "probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the SDHH encoding sequences." Upon reading this specification, one of skill in the art would recognize that "at least 50% sequence identity" would encompass the 90% variants recited by the claims. The skilled artisan would also understand that the claimed variants would be useful as probes regardless of the enzymatic activity or lack thereof of the encoded protein. The specification further discloses the use of polynucleotide sequences in microarray technology (specification, p. 37, line 32 to p.38, line 6). This technology can be used to

"identify genetic variants, mutations, and polymorphisms" (specification, p. 38, line 3). One of skill in the art would recognize that the information gained in these types of experiments could be useful in determining gene function, understanding the genetic basis of a disorder, or to diagnose a disorder. The experimental processes employed would be the same regardless of whether the polypeptide encoded by the polynucleotide sequence used in the microarray possessed enzymatic activity.

The specification further discloses that "[t]he polynucleotide sequences encoding SDHH may be used in Southern or Northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and ELISA assays; and in microarrays utilizing fluids or tissues from patients" (specification, p. 36, lines 13-16). Methods of using polynucleotides such as those encoding SDHH are well known in the art, and guidance for these methods is also provided throughout the specification (e.g., p. 37, lines 18-31; p. 47, lines 16-33; p. 48, lines 1-20). Thus one of ordinary skill in the art would know how to use the claimed polynucleotide variants encoding SDHH with or without enzymatic activity.

Furthermore, Applicants submit with this paper the Declaration of Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Office Action with respect to the enablement of the claimed polynucleotides and their naturally occurring variants are without merit.

This United States patent application is a divisional application of and claims priority to United States patent application Serial No. 09/088,435, filed in the names of Preeti Lal et al. on June 1, 1998 (hereinafter "the Lal '435 application"), having essentially the identical specification, with the exception of corrected typographical errors and reformatting changes. Thus page and line numbers may not match as between the instant application and its parent application. Dr. Bedilion cites to the parent application (Lal '435) in his Declaration.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their

activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would appreciate that cDNA microarrays that contained the claimed polynucleotides, including the SEQ ID NO:2 polynucleotide variant would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating disorders of metabolism and cancer for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-June 1, 1998 publications showing the state of the art on June 1, 1998 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts(a)-(f), he specifically states that his explanations are not "all-inclusive" (Bedilion Declaration, ¶ 15). For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on June 1, 1998 (and for several years prior to June 1, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Lal'435 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Lal '435 application at the time it was filed "would have wanted their cDNA microarray to have the claimed polynucleotides, including the SEQ ID NO:2 polynucleotide variant because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 1, 1998 (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Lal '435 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec. 681, No. 8 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107

Environ. Health Perspec. 681, No. 8 (1999). One of skill in the art would recognize that the most powerful arrays would therefore include naturally occuring polynucleotide variants (e.g. single nucleotide polymorphisms, allelic variants, etc.) whether or not those variant polynucleotides encoded a functional protein.

As stated above, the specification discloses many uses of the claimed polynucleotides, including the SEQ ID NO:2 polynucleotide variants. Further, the Bedilion Declaration specifically describes the use of the claimed polynucleotides in microarray technology. This technology was well known in the art at the time that the instant application was filed, as evidenced by the publications cited by Dr. Bedilion as well as the disclosure in the specification, for example at p. 35, lines 21-26. Thus, one of skill in the art, upon reading this specification, would know how to use SDHH-encoding polynucleotides. Furthermore, one of skill in the art would recognize that the use of a *naturally occurring variant* SDHH-encoding polynucleotide would be the same, whether or not the encoded variant SDHH protein had enzymatic activity.

For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Written description rejections under 35 U.S.C. § 112, first paragraph:

Claims 3, 6-7, 9, and 11 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention, at the time the application was filed.

The Examiner states that "the claims recite serine hydratase activity not serine dehydratase activity and as such one skilled in the art would not know how to test the polypeptides for activity" (Final Office Action, p. 4). As stated in the previous section, the amendment of 3/18/03 which amended claims 3 and 9 to recite a biological activity of serine hydratase rather than serine dehydratase was a typographical error. The present amendments to claims 3 and 9 correct that typographical error.

With respect to the written description of the claimed variants of SEQ ID NO:2, the Examiner states that "the general knowledge in the art does not provide any indication of how the structure of one

variant is representative of unknown variants" (Final Office Action, p. 4). Applicants respectfully emphasize that the claimed variant polynucleotides are "naturally occurring" and as such, the scope of the claimed variants in narrowed to a finite set, rather than all possible variants that could be produced using recombinant DNA techniques. The specification describes several types of naturally occurring variants (e.g., allelic variants and altered nucleic acid sequences). An "allelic variant is described as "an alternative form of the gene encoding SDHH. Allelic variants ... may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered" (specification, p. 6, lines 13-16). "Altered" nucleic acid sequences are described as "sequences with deletions, insertions, or substitutions of different nucleotides" (specification, p. 6, line 21 to p. 7, line 4). These descriptions underscore that the claimed polynucleotide variants are limited to "*naturally occurring*" polynucleotide variants and provide guidance as to what types of variants are encompassed in the claims.

The scope of the of the claimed variants is further limited by the recitation in the claims of a polynucleotide "at least 90% identical to the polynucleotide sequence of SEQ ID NO:2" or encoding a polypeptide "at least 90% identical to the amino acid of SEQ ID NO:1." The specification discloses the sequences of SEQ ID NO:1 and SEQ ID NO:2 (specification, pp. 54-55). The specification also provides guidance in determining percent identity (specification, p. 10, lines 11-27). These and other methods are also well known in the art. One of skill in the art would therefore readily recognize a polynucleotide variant having 90% identity to SEQ ID NO:2 or to a polynucleotide encoding SEQ ID NO:1.

Applicants submit that with the disclosure of the sequences of SEQ ID NO:1 and SEQ ID NO:2, the recitation of "naturally occurring" and "at least 90% identical" in the claims, and the routine use of sequence comparison analysis methods by persons of skill in the art, the claimed polynucleotide variants are adequately described. As stated in Section 2163.02 of the Manual of Patent Examining Procedure "one must define a compound by 'whatever characteristics sufficiently distinguish it.'" Persons of skill in the art routinely use percent identity of one sequence to another to describe a sequence. Applicants submit that the percent identity limitation coupled with the limitation that the variant be "naturally occurring" would serve to adequately describe to one of skill in the art the claimed variants so as to sufficiently distinguish them from other unrelated sequences.

Withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph is therefore respectfully requested.

New Grounds of rejections - written description rejections under 35 U.S.C. § 112, first paragraph:

Claims 3-7, 9, and 11 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time that the application was filed.

The Examiner states that "[c]laims 3 and 9 have been amended to recite 'has serine hydratase activity'. The response filed 3/18/03 did not state where support can be found in the specification." Applicants submit, as stated in previous sections above, that the amending of claims 3 and 9 to recite "serine hydratase" rather than "serine dehydratase" was merely a typographical error, which the present amendments correct. As amended herein, claims 3 and 9 now recite "serine dehydratase" activity. These amendments add no new matter as there is ample support in the specification for serine dehydratase activity. The Examiner concedes that "the specification has support for serine dehydratase activity (see page 50)" (Final Office Action, p. 6).

Withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney/Agent below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**, as set forth in the enclosed fee transmittal letter.

Respectfully submitted,
INCYTE CORPORATION

Date: July 21, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims **3** and **9** have been amended as follows:

3. (Thrice Amended.) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine dehydratase [hydratase] activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1.

9. (Thrice Amended.) A method of producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine dehydratase [hydratase] activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1, the method comprising:

i) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding said polypeptide, and

ii) recovering the polypeptide so expressed.